REMARKS

Claims 75-115 are pending in the present application. Claims 75-78 are withdrawn. Claims 79-115 were examined.

Reconsideration of the present application is respectfully requested.

Rejection under 35 USC § 103

The Examiner has rejected claims 79-115 as unpatentable over Romanczyk, Jr. (US 5,554,645) in view of Faendriks (Derwent Acc No 1997-525196, abstract) on the ground that Romanczyk teaches a food composition comprising a cocoa polyphenol, and Faendriks *et al* teach use of L-Arginine, respectively, for the same purpose (anti-cancer/tumor) and it would have been obvious to combine the two active ingredients into one composition for anti-cancer treatment and that adjustment of the amounts/ranges of each active ingredient is deemed merely a matter of judicious selection and routine optimization to arrive at the claimed compositions. Applicants respectfully traverse the rejection.

New Rejection is cumulative:

At the outset, Applicants submit that the present rejection is cumulative over the previously withdrawn rejection over the combination of Romanczyk, Jr. (US 5,554,645) and Wideman *et al*. (US 6,127,421). The Examiner cited Romanczyk and Wideman on the ground of teaching cocoa polyphenol and L-arginine, respectively for anti-cancer/tumor purposes. Applicants' claim amendment to recite a specific numerical range of cocoa polyphenol in the composition thus making the composition effective for vasorelaxation (*i.e.*, "up to 3 g of cocoa polyphenol"), and arguments with additional evidence provided, were found persuasive by the Examiner and the above rejection was withdrawn (*see*, Amendment and Response filed December 24, 2009, and June 14, 2010; of record). Now, the Examiner appears to have imposed the same rejection by substituting Wideman with Faendriks, both for teaching L-arginine. On this ground alone, the rejection should be withdrawn. Nonetheless, Applicants address the new rejection below.

As per Applicants' amendment filed December 24, 2009 claims recite the limitation of the "product comprises up to 3 g of cocoa polyphenol per unit dose." In this regard, Applicants note that the Examiner had cited Romanczyk U.S. 5,554,645 and Faenrdiks with respect to anti-neoplastic (anti-cancer) utility.

The claim limitation of up to 3g of cocoa polyphenol must be given weight:

With respect to Romanczyk's teaching, Romancyzk neither discloses numerical amounts of cocoa polyphenols needed for anti-neoplastic effects nor does he suggest their effectiveness for achieving vasorelaxation (vasodilation). Thus, in absence of any suggestion or guidance with respect to numerical amounts (for anti-neoplastic effects), a person of skill in the art reading Romanczyk would not have had any starting reference point to optimize amounts of cocoa polyphenol for the vasodilating effects recited in the present claims. This is discussed in more detail below.

Faendriks does not teach the use of L-arginine for the "same purpose" as Romanczyk

Regarding Faendriks, Applicants submit that Faendriks does not teach the use of L-arginine for the "same purpose" as Romanczyk. Faendriks teaches the use of L-arginine for treatment of infections caused by *Helicobacter pylori* (*see*, *e.g.,* Faendriks, Abstract, and WO 98/57626). While Faendriks mentions that *Helicobacter pylori* infections can be considered an important factor in stomach cancer and stomach lymphoma, the purpose of Faendriks is not to treat stomach cancer, rather to achieve "eradication of the bacteria" and thus cure the ulcer disease (*see*, Faendriks WO 98/57626, page 1, lines 15-19). Therefore, a person of skill in the art would not have had any reason to combine Faendriks with Romanczyk for the treatment of cancer.

Effects of L-arginine as an anti-tumor ingredient were unpredictable

Based on knowledge in the art as of the effective filing date of the present application, effects of L-arginine as an anti-tumor ingredient were unpredictable, and therefore provided no reasonably expectation of success for anti-tumor treatment using L-arginine. To illustrate this point, Applicants enclose herewith a lecture by Kenneth Park entitled "The Immunological and Metabolic Effects of L-arginine in Human Cancers"

(Attachment 1, Proc. Nutrit. Soc. 52,387-401 (1993)), in which studies in animals and humans with cancer showed that L-arginine supplementation stimulated tumor growth and tumor protein synthesis, respectively. That the knowledge in the art as to the anti-tumor/cancer effect of dietary arginine supplementation in mammals was highly controversial is further illustrated for example, in Yeatman T. J. *et al.* Depletion of Dietary Arginine Inhibits Growth of Metastatic Tumor, *Arch. Surg.* 1991, 126(11):1376-82 (Attachment No. 2). Using a mouse (mammalian) model, Yeatman showed that dietary arginine depletion inhibited the growth of liver metastases of colorectal cancer cells. Thus, Yeatman teaches away from the use of dietary arginine supplementation to inhibit tumor/cancer growth, therefore a person of skill in the art would not have been motivated to modify the food of Romanczyk by adding L-arginine with any reasonable expectation of success that both the polyphenol and L-arginine would have had anti-tumor effects.

Applicants thus submit that, as of the effective filing date of the present application, contradictory evidence existed regarding the role of L-arginine in tumorigenesis, hence, one of skill in the art could not have predicted the anti-tumor behavior of L-arginine supplied as a human or veterinary food (as required by the present claims) with a reasonable expectation of success of achieving the recited vasodilating effects. In view of the uncertainty in the art, a person of skill in the art would not have known if L-arginine would have had an anti-tumor effect and therefore would have had no reason to combine it with cocoa polyphenol and have any reasonable expectation of success.

Routine optimization of prior art taught away from the dosage levels of the present composition:

As of the effective filing date of the present application, polyphenol art taught high dosages (>10 g of polyphenol, *e.g.,* quercetin) were required for achieving anti-neoplastic benefits (*see*, Attachment 3- Molnar *et al*, "Antitumor activity of flavonoids on NK/Ly ascites tumor cells." *Neoplasma*, vol. 28, issue 1, 11-18. 1981). For example, antineoplastic effects of quercetin were tested in mice at dosages of 40 mg/kg/day, which

dosage was associated with a 20% increase in subject life span. However, increasing the dosage was considerably more effective—quercetin at a dosage of 80 mg/kg twice daily (*i.e.,* 160 mg/kg) was found to be more effective—at this higher dose, 94% increase in subject life span was observed (*see,* Attachment 3- Molnar *et al.*). It is true that quercetin is a distinct compound from cocoa polyphenols recited in Applicants' claims but once cocoa polyphenols were discovered by Romanczyk to have antineoplastic properties like quercetin, one skilled in the art would have then expected that high dosages were important for the effect and would not have optimized the dose downward, *i.e.,* to arrive at the amounts recited in Applicants' claims. Assuming an average person of 70 kg, the optimum quercetin dosage of 160 mg/kg results in a dosage of 11.2 g of quercetin. In contrast, Applicants claims recite "up to 3 g of cocoa polyphenol." There is nothing in the cited art to suggest to a person of skill in the art to prepare compositions with a reduced amount of polyphenol per unit dose.

In order to make a claimed quantity obvious and "merely a matter of judicious selection and 'routine optimization'" the prior art must show that adjustment to the claimed amount is an **optimization of the prior art** (*Ex parte Buzzoni*, applicants respectfully provide the citation to the case: No. 2007-3725, slip op. (B.P.A.I., January 30, 2008)[1]. In other words, the prior art should have suggested vasodilating effects of recited compounds before the experiments to optimize the amount of the compounds to achieve vasodilating effects could have been conducted. The knowledge of vasodilating effects is crucial because (as shown in Molnar *et al.*), optimizing the amount of cocoa polyphenol for cancer application would have led a person of skill in the art away from the low dosages recited in Applicants' claims.

"[A] particular parameter must first be recognized as a result-effective variable, *i.e.,* a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." *(see,* MPEP Section 2144.05 II). Consequently, in order to make the claimed compositions obvious, the cited references (Romanczyk and Faendriks) should have recognized that cocoa polyphenols of Romanczyk are effective for inducing

[1] Applicants have not provided a copy of this case, because they believe it is readily available to the Examiner. Should the Examiner require a copy, the Examiner is invited to telephone the undersigned.

vasodilation (rather than for anti-neoplastic effects). In other words, a person of skill in the art would have had no reason to optimize the amounts of cocoa polyphenols of Romanczyk to achieve vasodilating effects and have any reasonable expectation of success when such effects were not suggested by any of the cited references. This is because "the prior art [must] have suggested 'the kind of experimentation necessary to achieve the claimed composition" *In re Boesch*, 617 F.2d at 276 (holding that such a showing was made). *See also, In re Antonie*, 559 F.2d at 620 (holding that such a showing was not made). In *In re Antonie,* the claims at issue recited a wastewater treatment device comprising a tank having certain "treatment capacity" which capacity was a function of "tank volume." The prior art cited by the Patent Office disclosed the basic structure of Antonie's device but was silent regarding the "tank volume." The Court reversed the rejection because the cited prior art "was not trying to maximize or control 'treatment capacity';" "experiments suggested by [the cited art did] not reveal the property which applicant [had] discovered;" and "there [was] no evidence in the record that the prior art recognized that particular parameter affected the result." *Id.*

Following the reasoning in *Antonie* and *Boesch,* Romanczyk and Faendriks should have suggested, to a person of skill in the art, vasodilating effects of their compounds before the experiments to optimize the amount of these compounds in a composition that achieves the vasodilating effect could have been conducted. In the absence of such a recognized result, and further because other knowledge in the art (*see* Attachment 3, Molnar) suggested that polyphenol doses should be increased to optimize the anti-neoplastic effects, arriving at the amount limitations of Applicants' present claims would not have been the result of routine optimization. In fact, based on Romanczyk and Faendriks, a person of skill in the art would not have expected the composition recited in Applicants' claims to be useful.

This conclusion is further supported by the recent decision of the USPTO Board of Appeals and Interferences, which is also on point. In *Ex parte Buzzoni* (BPAI Appeal No. 2007-3725, U.S. Appl. Ser. No.: 10/183,478, pages 6-7 (2008)), the Appellant claimed an anchorless wheel bumper block (to be used as a stop in a parking facility), and the cited prior art disclosed a cellular arresting block (for use to slow and stop aircrafts,

trucks and other vehicles). The prior art block was larger than the claimed block and the Examiner rejected the claims on the ground that it would have required routine optimization to modify the block of the prior art and arrive at the claimed block. The Board disagreed and held that the Examiner failed to establish a *prima facie* case of obviousness because he failed to establish that an optimum obtained for the cited prior art block would have also been an optimum for the Appellants' block. Here, applying *Buzzoni* to the facts of the present case, dosage optimum for anti-tumor purposes is not the same as dosage optimum for vasorelaxation purposes recited in Applicants' claims. In other words, even if one were to assume, for purposes of an argument, that it would have been obvious to optimize the amounts of compounds taught by Romanczyk and Fanedriks for anti-tumor purposes; the Examiner has not established (and could not have as shown above) that it would have been obvious to optimize the amounts of the compounds and arrive at those recited in the rejected claims.

The recitation "effective to induce vasorelaxation in a human or a veterinary animal" is a structural claim limitation

The Examiner states that no weight is given to the claim recitation "effective to induce vasorelaxation in a human or a veterinary animal" because it only refers to the intended use of the composition. The Examiner actually refers to a limitation not found in the present claims, but Applicants address the Examiner's comment vis-à-vis the above claim recitation.

Applicants submit that the above recitation structurally defines the composition as it requires that the non-chocolate product per unit dose has the required amounts of cocoa polyphenol and L-arginine to induce vasorelaxation. This structurally differentiates Applicants' composition from any other combination of cocoa polyphenol and L-arginine, which does not achieve the recited effect.

In summary, the expectation that high dosages were required for anti-tumor treatment would have, at best, lead to upward optimization of Romanczyk and Faendriks resulting in much higher amounts per unit dose than those presently claimed and a *prima facie* case of obviousness has not been made, because not knowing vasodilating

properties of cocoa polyphenols, a person of skill in the art would not have had any reason to adjust the amounts downward to arrive at the products recited in the present claims.

Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above remarks, Applicants believe that the application is in condition for allowance. An action to that effect is respectfully requested.

Respectfully submitted,

Date: **January 17, 2011**

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